Pharmacy and Wellness Review

Volume 7 | Issue 3 Article 4

January 2016

Use of Botulinum Toxin in Central Nervous System Disorders

Julie Puvogel
Ohio Northern University

Paige Torbet
Ohio Northern University

Jourdan Ujlaki
Ohio Northern University

Rebecca Worden
Ohio Northern University

Lindsey Peters
Ohio Northern University, l-peters@onu.edu

Use of Botulinum Toxin in Central Nervous System Disorders

Julie Puvogel, Paige Torbet, Jourdan Ujlaki, Rebecca Worden, Lindsey Peters, PharmD, RPh, BCPS

Abstract

Botulinum toxin is a neurotoxin that is produced by Clostridium botulinum. At one time, this toxin was only seen as a lethal substance, but now scientists have found many medical uses for it. There are eight distinctive toxins (A-H), but only A and B currently have clinical uses. Botulinum toxin A has three different versions that are U.S. Food and Drug Administration (FDA) approved: onabotulinumtoxinA (Botox®), abobotulinumtoxinA (Dysport®), incobotulinumtoxinA (Xeomin®). Botulinum toxin B is also FDA approved as rimabotulinumtoxinB (Myobloc®). The toxins work by inducing reversible, local, dose-dependent chemodenervation by inhibiting acetylcholine release from presynaptic terminals. These drugs are approved to treat many different types of disorders but have found significant use for the treatment of migraines, dystonias and cerebral palsy. Botulinum toxin has proven to be efficacious in prophylactically treating those patients with migraines who have failed other pharmacologic and nonpharmacologic treatments. Botulinum toxin is also FDA approved for the treatment of dystonias; more specifically, all three types of botulinum toxin A and the rimabotulinumtoxin B have FDA approval for the treatment of cervical dystonia. Perhaps the most important use for botulinum toxin is in patients with cerebral palsy. Botulinum toxin is efficacious in patients with upper limb spasticity who are not good surgical candidates. It also proves useful as an adjunct to physiotherapy in these patients. This can help reduce or slow progression in patients with cerebral palsy. Exercise has been shown to be an efficacious treatment in patients with migraines, dystonias and cerebral palsy. Further research is necessary to determine the potential benefits the combination of exercise and botulinum toxin can have in these patients. While the high cost of botulinum toxin might deter some patients, it is a good option for those that have exhausted other options or are not good candidates for surgery.

Key Terms

Acetylcholine; Acetycholine Release Inhibitors; Botulinum Toxins Type A; Cerebral Palsy; Chronic Disease; Clostridium botulinum; Migraine Disorders; Muscle Spasticity; Nerve Block; Neurotoxins; Pharmaceutical Preparations; Physical Therapy Modalities; Presynaptic Terminals; Torticollis

Introduction

The application and knowledge of botulinum neurotoxin has increased exponentially since its first documentation in 1815 by Professor Johann Heinrich Ferdinand Autenrieth.[1] Justinus Kerner made the first major breakthrough in the understanding of botulinum toxin several years later in 1822. Kerner found and recorded the symptoms of the toxin, hypotheses of pathophysiology and the idea that there were therapeutic uses for the toxin. Due to the human body's response to botulinum toxin, Kerner proposed that small amounts should "reduce or block the hyperactivity and hyperexcitability of the motor and autonomic nervous system."[1] Since this publication, several researchers have expanded upon this concept. The explorations of these researchers have resulted in the first successful application of the gastric tube, the discovery of botulinum toxin-producing bacteria (Bacillus botulinus, later named Clostridium botulinum) and many additional therapeutic uses of botulinum toxin, some of which are examined below. In this article, botulinum toxin will be described including which preparations are currently available. The specific uses of botulinum toxin will be identified, and clinical trials will be evaluated for botulinum toxin use in the diagnoses and treatment of migraines, dystonias and cerebral palsy. The progression in the understanding of this toxin is evident as scientists have utilized a toxin that was once lethal to now treat numerous disorders and improve the quality of many lives. Further research will only continue to unveil new opportunities for the medical use of botulinum toxin.

Botulinum Toxin

Botulinum toxin is produced by Clostridium botulinum and includes eight antigenically distinct toxins, labeled A through H.[2] Botulinum toxin is composed of a core neurotoxin and many nontoxic accessory proteins which protect and stabilize it from temperature changes, variable pH and enzymatic degradation. The toxin is activated after secretion by scission, either with endogenous or exogenous proteases, and is then able to induce reversible, local, dose-dependent chemodenervation by inhibiting acetylcholine release from presynaptic nerve terminals. The binding domain of the toxin binds to presynaptic nerve endings and is internalized via endocytosis. The catalytic domain, a zinc endopeptidase, is released in the cytoplasm and irreversibly cleaves proteins that are essential for regulating exocytosis. This prevents the acetylcholine vesicles from fusing with the plasma membrane, thus preventing the release of acetylcholine into the synaptic cleft. It takes approximately three months for new exocytosis regulating proteins to be resynthesized, which leads to a full recovery of the neuromuscular junction.

After years of clinical use and repeated injections of botulinum toxin, sensitization has been known to occur.[2] This sensitization is due to the formation of anti-botulinum toxin antibodies. These antibodies can be targeted against the core of botulinum toxin resulting in complete inhibition of the toxin. However, there can also be antibodies that are targeted against proteins in the toxin and therefore not interfere with the toxin's biological activity. The formation of these antibodies is the

main reason to be cautious when using botulinum toxin, as these antibodies can cause adverse effects for the patient.

There are four main botulinum toxins used as pharmaceuticals: onabotulinumtoxinA (Botox®), abobotulinumtoxinA (Dysport®), incobotulinumtoxinA (Xeomin®) and rimabotulinumtoxinB (Myobloc®).[2] They differ in purity, potency, immunogenicity, complexity and manufacturing.

There are many U.S. Food and Drug Administration (FDA) indications for the use of botulinum toxin (summarized in Table 1).[3] Botulinum toxin is considered a first-line treatment in patients with cervical dystonia (CD) which presents as a combination of dystonic movements and postures and, frequently, pain.[2] The first choice of therapy for patients with blepharospasm, an involuntary closure of the eyelids, is also botulinum toxin; safety and efficacy have been proven in clinical trials. There is also strong evidence in support of using botulinum toxin for upper limb spasticity. A common FDA approved indication is the treatment of glabellar lines, more commonly referred to as "frown lines."[3] Other indications vary according to which toxin is being used. OnabotulinumtoxinA has the most indications, other than those already mentioned, including axillary hyperhidrosis, chronic migraine, lateral canthal lines, lower limb spasticity, overactive bladder, strabismus and blepharospasm associated with dystonia and urinary incontinence due to detrusor overactivity.[3]

Adverse reactions to botulinum toxins can occur.[3] The incidence of the adverse reaction depends on what the toxin is being used to treat as well as the brand of the toxin. Some more prominent adverse reactions that have been reported to be caused from botulinum toxin include urinary tract infection, urinary retention, headache, neck pain, injection site irritation, upper respiratory tract infection, dizziness and strabismus. Botulinum toxin is associated with an administration warning: botulinum toxin can spread beyond the site of injection and can cause life threatening injury such as dysphagia.

Botulinum toxin is dosed in units, and it is recommended that the lowest dose should be used when initiating treatment and increasing the dose as necessary to alleviate symptoms of disease.[3] No dose adjustments are required for patients with renal or hepatic impairment. The onset of ac-

Table 1. A Summary of Available Botulinum Toxins.[3]

Generic Name (Brand Name)	AbobotulinumtoxinA (Dysport®)	IncobotulinumtoxinA (Xeomin®)	OnabotulinumtoxinA (Botox®)	RimabotulinumtoxinB (Myobloc®)
Botulinum Toxin Type	Type A	Type A	Type A	Type B
Labeled Indication(s)	Cervical dystonia; glabellar lines (moderate to severe)	Blepharospasm, cervical dystonia, glabellar lines (moderate to severe), upper limb spasticity	Axillary hyperhidrosis (severe); blepharospasm associated with dystonia; cervical dystonia; migraine (chronic) prophylaxis; overactive bladder; strabismus; upper limb spasticity (severe); urinary incontinence (due to detrusor overactivity associated with a neurologic condition) Cosmetic: Glabellar and lateral canthal lines (moderate to severe)	Cervical dystonia
Dosage Forms Available	Injection, powder for solution	Injection, powder for solution	Injection, powder for solution	Injection, solution
Dosage Strengths Available	300 and 500 units	50, 100 and 200 units	100 and 200 units	2,500 units per 0.5 mL; 5,000 units per 1 mL; 10,000 units per 2 mL
Route of Administration	IM	IM	IM, intradermal, intradetrusor	IM

Adapted from: Lexicomp [Internet]. Hudson (OH): Wolters Kluwer. 2016.

tion, represented by improvement of symptoms, can occur anywhere from days after injection to weeks after injection and is dependent on the toxin used. The toxin typically has a duration of months but is also dependent on toxin used and indication.

It should be noted that botulinum toxin is costly. Depending on the brand, botulinum toxin can cost around $700 for 100 units.[3] Insurance coverage varies, though most insurances require a patient to be nonresponsive to at least one treatment prior to trying botulinum toxin.[4] In light of this, cost can be a major barrier to treatment for patients and should be weighed against other, less-costly treatment options.

A review follows of the current nonpharmacologic and pharmacologic treatment options for the three common indications: migraine, dystonia and cerebral palsy. An evaluation of the literature for both safety and efficacy is also included. A summary of the trials discussed is shown in Table 2.

Migraines

The prevalence of migraines varies by age and gender, but in the United States it is reported that more women than men experience migraine headaches.[5] It has been reported that prevalence is highest in patients between 30 and 49 years of age.

The etiology and pathophysiology of migraines are not completely understood, however, most clinicians believe the pathogenesis may be related to complex dysfunctions in neuronal and broad sensory processing.[5] The pain due to migraines is thought to come from activity within the trigeminovascular system, which is a network of visceral afferent fibers arising from the trigeminal ganglia and projects peripherally to innervate pain sensitive cranial blood vessels, dura mater and large venous sinuses. These fibers also project centrally where they terminate in the trigeminal nucleus caudalis in the brainstem and upper cervical spinal cord providing a pathway for nociceptive transmission to the higher centers of the central nervous system (CNS). Activation of trigeminal sensory nerves releases vasoactive neuropeptides, which interact with dural blood vessels to promote vasodilation and dural plasma extravasation, causing neurogenic inflammation. Conduction along the trigeminovascular fibers transmits pain inputs to the trigeminal nucleus caudalis where the pain information is relayed to higher pain centers. Continued afferent input can cause sensitization of the central sensory neurons which produces a state that maintains the headache. It is thought that those who experience migraines have a lower threshold of response to specific environmental factors that govern the balance of CNS excitation and inhibition. The responsiveness of the migrainous brain may be due to genetic factors that cause abnormalities in ion channels and pumps that control the release of neurotransmitters in the brain.

Treatment strategies for migraines are generally individualized, based on the patient's long-term and short-term goals, and usually aim to minimize headache-related disability and distress to improve the patient's quality of life.[5] In general, treatment includes both pharmacologic and nonpharmacologic options that are both prophylactic and symptomatic and depend on the severity of the migraine. It is noted when migraine medications are used frequently and/or excessively, a phenomenon occurs in which the headache symptoms recur with increased frequency or intensity. This is known as "rebound headaches" or "medication overuse" headaches. No specific treatments have been shown to be effective for this other than tapered withdrawal of the medications being overused.

Nonpharmacologic treatment for migraines can include keeping a headache journal to identify triggers to avoid, performing behavioral interventions such as relaxation therapy, and adhering to a general wellness program including sleep, exercise, healthy eating, smoking cessation and limiting caffeine intake.[5] The effects of aerobic exercise and yoga on migraine severity and recurrence are based on limited research. According to a review of literature on these and other alternative treatment methods, studies have found opposing results, but recent research has shown positive effects on reduction of migraine symptomology.[6] In a study of 72 patients with migraines, headache intensity, medication use and pain ratings were found to be significantly lower ($P < 0.001$) in the group who completed 12 weeks of 60 minutes of yoga five times a week versus the control group.[7] Additionally, the intervention group displayed a significant decrease in anxiety and depression ($P < 0.001$). A Turkish study examined the relationship between migraines and aerobic exercise delivered in three (one hour) sessions per week and reported that the severity, frequency and duration of migraines were decreased with regular activity compared to the control group.[8] Additional information regarding these and alternative treatment methods can be obtained from Karakurum Göksel's review of therapeutic options for migraine patients.[6] Due to the lack of research on these topics, the combination of botulinum toxin and exercise has not been examined. Further research should be conducted to determine whether the benefits of each treatment can be additive or synergistic for greater gains in symptom relief.

Common pharmacologic treatments include analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs).[5] Serotonin receptor agonists, such as sumatriptan, are also used as migraine relief medications. Migraine relief is a result of normalizing dilated intracranial arteries, inhibiting vasoactive neuropeptide release and inhibiting transmission to the thalamus. Beta adrenergic antagonists are most widely used for migraine prophylaxis. While the precise mechanism of how this class of drug prevents migraines is unknown, it is thought that they may raise the migraine threshold by modulating adrenergic or serotonergic neurotransmission in cortical or subcortical pathways. Antidepressants are also potentially beneficial in migraines most likely due to the downregulation of central serotonin receptors, increased levels of synaptic norepinephrine and enhanced endogenous opioid receptor actions. Anticonvulsants are emerging as an option in treating migraines, especially in patients who also

Table 2. Summary of Studies Discussed.

Authors	Study Design	Disease State Studied	Main Endpoints	Author's Conclusions
Dodick DW, Mauskop A, Elkind AH, et al.[4]	Randomized, double-blind, placebo controlled	Migraines	Change in number of headache days	Botox® is an effective prophylactic treatment in migraine patients who are not using any other prophylactic migraine medications.
Jankovic J, Adler CH, Charles D, et al.[14]	Prospective, observational, multicenter registry	Cervical Dystonia	Clinical safety and efficacy of onabotulinumtoxinA in cervical dystonia	OnabotulinumtoxinA is safe and efficacious in the treatment of cervical dystonia.
Evidente VGH, Fernandez HH, LeDoux MS, et al.[15]	Randomized, double-blind, repeated-dose	Cervical Dystonia	Efficacy and safety of incobotulinumtoxinA for cervical dystonia in repeated doses	IncobotulinumtoxinA is safe and efficacious in the treatment of cervical dystonia.
Truong D, Brodsky M, Lew M, et al.[16]	Randomized, double-blind, placebo controlled	Cervical Dystonia	Long-term efficacy and safety of Dysport®	Dysport® is safe and efficacious in long-term treatment of cervical dystonia.
Dressler D, Tacik P, Saberi FA[17]	Prospective, open-label crossover study	Cervical Dystonia	Comparing potency of the drugs Botox® and Xeomin®	Similar therapeutic effect durations; doses were exchanged at a 1:1 ratio, concluded similar efficacy and potency.
Yun JY, Kim JW, Kim HT, et al.[18]	Randomized, double-blind, multicenter, non-inferiority, two-period crossover study	Cervical Dystonia	Compared Dysport® and Botox® by looking at changes in TWSTRS and Tsui scale scores	No significant difference between groups in the TWSTRS ratings or the Tsui scale; concluded that Dysport® and Botox® are comparable at dosage conversion of 2.5:1.
Koman LA, Smith BP, Williams R, et al.[24]	Randomized, double-blind, placebo-controlled	Cerebral palsy (upper limb)	Assess efficacy of botulinum toxin A on Upper Extremity Rating scale, HC, Modified House Functional Classification and Melbourne Assessment of Unilateral Upper Limb Function of patients	Those that received therapy had statistically significant improvement in the Melbourne Assessment compared to placebo, authors concluded that it was safe and a good option for patients who are not good candidates for surgery.
Ferrari A, Maoret AR, Muzzini S, et al.[25]	Randomized placebo-controlled	Spastic hemiplegic upper limb cerebral palsy	Study the effects of botulinum toxin combined with physiotherapy measured by the Assisting Hand Assessment (AHA)	Botulinum therapy was significantly better than placebo when combined with physiotherapy.

experience seizures, anxiety and bipolar illness. These agents are thought to be beneficial due to the modulation of the excitatory neurotransmitter glutamate and inhibition of sodium and calcium ion channel activity.

Botulinum toxin has been shown to inhibit the release of nociceptive mediators, causing anti-nociceptive action separate from its neuromuscular activity.[5] Also, botulinum toxin has been shown to inhibit sensitization of central trigeminovascular neurons, which is felt to be important in the development, progression and maintenance of migraines. Thus, botulinum toxin has been an area of research for prophylaxis of migraine headaches.

A randomized, double-blind, placebo-controlled study of 355 patients experiencing 16 or more headache days during a 30-day baseline period was conducted.[4] The study included a 30-day baseline period, followed by a 30-day, single-blind, placebo-run-in period in which placebo response was determined, followed by a nine month, double-blind treatment period in which patients received three treatment cycles of either Botox® or placebo, separated by 90 days. During the study, characteristics of the patient's headaches were recorded using an electronic telephone diary. The participants in the study were grouped into those taking prophylactic medications and those that were not. Of those that were not taking any prophylactic medication, 117 received the botulinum toxin and 111 received placebo. Analysis of these 228 patients was conducted. At baseline, the number of headache-free days between these placebo and treatment groups were similar. The increase in headache-free days for the botulinum toxin group was 10 days, compared to the placebo group of 6.7 days, and was statistically significant with a p-value of 0.038. Mean usual headache severity decreased over the course of the study for both the placebo and the treatment group. However, the decrease was greater in the botulinum toxin group and was statistically significant from day 180 to day 270. This study also evaluated the use of acute headache pain medication in addition to either the toxin or the placebo. It was found that there was a statistically significant difference between the placebo and toxin group in the use of pain medication. The placebo group decreased by only 4.1 days, compared to the toxin group, which decreased its use of pain medication an average of 7.8 days. This study showed that headache symptoms improved in patients receiving botulinum toxin in all efficacy parameters studied.

In another study, Mitchel and colleagues looked into the cost-effectiveness and quality of life (QOL) improvements in using botulinum toxin to treat refractory migraine headaches.[9] Surveys were sent to 54 patients, and 32 were returned. The survey included six QOL measures: headache severity, headache frequency, use of rescue medications, productivity/absenteeism, recreational activities and life enjoyment. Participants used a five-point scale to assess those categories, which were no improvement, little improvement, moderately improved, quite a bit improved, or extremely improved. A composite QOL score was calculated by summing up the measures for each category, and 73 percent of participants reported moderate or better improvement in overall migraine QOL measures. However, analysis of total migraine-related pharmacy costs (cost of the toxin and overall migraine-related medications) shows that costs went up by 80.9 percent after initiating toxin treatment. There was no change in the number of migraine-related emergency room visits. Limitations with this study include a short follow-up period, the use of concomitant pain medications and no comparison group.

For the treatment of chronic migraines, botulinum toxin appears to be as effective as current therapy, with a decreased need for additional pain medications. More large scale research needs to be performed with standardization of injection site location and dosage to solidify efficacy and safety of the toxin and determine if there is a place for using the toxin to treat refractory migraines.

Dystonias

Dystonia is a type of prolonged muscle tone that presents in patients in many different ways and can be mistakenly diagnosed as Parkinson's disease due to the repetitive and shaky movements with which some people present.[10,11] Due to the underdiagnosis of dystonia, often due to misdiagnosing, the true prevalence is hard to calculate.[10] The hallmark symptoms of dystonias are dystonic postures and movements (flexing or twisting movements, rigidity), sensory tricks (a trick is touching the affected body part to relieve dystonia), mirror dystonias (repetitive movements occur in a nonaffected limb) and overflow dystonias (dystonia occurring in an atypical body region for the patient).[11] The etiology is broken down into multiple parts, so it is important to classify the cause and type of dystonia in order to improve quality of life for the patient. The 2011 guidelines for dystonia provide a classification system to differentiate the types instructing clinicians to look at the etiology of the dystonia, the age of onset (early or late) and the distribution (focal, segmental, multifocal, generalized or hemidystonia).[10] Genetic testing can be done on symptomatic individuals to diagnose certain types of dystonia as well. For the most part, each type of dystonia has its own validated rating scale to evaluate the disease, monitor progression and predict impact on quality of life.

In general, nonpharmacologic treatment options that are utilized include occupational therapy, physical therapy, deep brain stimulation and selective peripheral denervation and myectomy.[12] Common medication classes that doctors prescribe for dystonias are skeletal muscle relaxants (especially intrathecal baclofen), anticholinergic drugs, anticonvulsant drugs, anti-dopaminergic drugs and dopaminergic drugs. The guidelines do suggest the use of botulinum toxin for different types of dystonias. As mentioned above, all three formulations of botulinum toxin A and botulinum toxin B are FDA approved for the treatment of cervical dystonia (CD).[10, 13]

OnabotulinumtoxinA (Botox®) had previously been the gold standard in cervical dystonia treatment. It was the first botulinum toxin that the FDA approved and has demonstrated

safety and efficacy in a prospective, observational registry that tracked 502 patients receiving Botox® for cervical dystonia.[14] IncobotulinumtoxinA (Xeomin®) is a newer preparation of botulinum toxin that does not have accessory proteins, which helps prevent possible immunogenicity problems. It, too, has shown to be efficacious and safe in a double-blind, repeated-dose 88 week study.[15] Similarly, the third type of botulinum toxin, abobotulinumtoxinA (Dysport®) demonstrated efficacy in a randomized, double-blind, placebo-controlled study, followed by an open-label extension.[16] Botulinum toxin B was noninferior to Botox® for the treatment of cervical dystonia in a randomized, double-blind, noninferiority trial.[13] Therefore, in today's practice, botulinum toxin B can be used as an alternative to botulinum toxin A.[10]

Because all three types of botulinum toxin A are safe and efficacious, studies are now comparing the different types. In a prospective, open-label crossover study comparing Botox® and Xeomin®, researchers compared the time between the injection and when the patient reported a decrease in the therapeutic effect.[17] They also compared the potency of the two drugs by giving participants at least four injection series of each drug at a 1:1 dose ratio. The mean time to decrease in therapeutic effect was 11.2 ± 1.1 weeks for Botox®, compared to Xeomin®, which had a time to decrease in effect of 11.4 ± 1.3 weeks. Researchers concluded that because there were similar therapeutic effect durations and that the doses were exchanged at a 1:1 ratio, Botox® and Xeomin® have similar efficacy and potency.

Similarly, researchers compared Dysport® and Botox® in a randomized, double-blind, multicenter, noninferiority, two-period crossover study.[18] The purpose of this study was to determine if a 2.5:1 ratio was an adequate conversion by looking at changes in the Tsui scale and the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) from baseline to follow-up (weeks 4, 8, 12, and 16). The Tsui scale is a short rating system that looks at sustained movement amplitudes, duration, shoulder elevation and dystonic tremor but does not assess how cervical dystonia affects a patient's daily life.[19] The TWSTRS is a validated scale that does look at the impact on a patient's life by summing up three different categories related to the participants' experience with cervical dystonia: severity, disability and pain.[16] They also evaluated the participants' preferences and the reasons for their preferences.[18] There was no significant difference between groups in the TWSTRS ratings, and while participants' ratings in the Tsui scale favored Botox®, the difference was not significant. When asked, more participants chose Dysport® (n=36) to Botox® (n=34), and 21 participants said they did not have a preference. In both cases of preference, the main reason that was given by patients was a perceived increase in efficacy. Adverse events were not statistically different between the two groups. Because neither version had a statistically significant preference, both drugs are comparable at a dosage conversion of 2.5:1 Dysport® to Botox®.

Since the three forms are all efficacious, safe and comparable, it is important to consider the cost-effectiveness to determine the best option for a patient. In a cost-utility analysis, authors compared Botox®, Dysport® and Xeomin® use in cervical dystonia from a federal government payer perspective. Outcomes were evaluated by measuring quality-adjusted life years (QALYs).[20] Assuming a willingness-to-pay value of $100,000 per QALY, all three formulations are considered cost-effective; however, the most effective was Xeomin® with a cost-effectiveness ratio of $27,548 per QALY, followed by Dysport® ($36,678), and Botox® ($49,337). The QALY gained in a one-year period was comparable with 0.06 QALY gained for Dysport® and 0.07 QALY gained for both Xeomin® and Botox®. The authors of the analysis also looked at wastage during injections because each manufacturer recommends using one vial per patient. Dysport® had the lowest wastage (2.2 percent) followed by Xeomin® (10 percent) and Botox® (22.9 percent). Xeomin® has an advantage over Botox®; it is available in 50 unit vials, whereas the smallest vial available for Botox® contains 100 units. The 50 unit vial allows for dose individualization with less waste. This analysis provides a useful comparison between the drugs from a cost perspective.

A current area of dystonia research surrounds the combination of exercise and botulinum toxin injections. Induced muscle weakness can result from botulinum toxin due to neuroparalysis and denervation.[21] Inclusion of treadmill training programs has been assessed in rats to examine the results of this combination. Researchers found that exercise diminished muscle atrophy following injections and positively affected muscle contractile strength recovery. There is a possibility that treadmill training could cancel out the response of spasticity reduction from the botulinum toxin injection. The current knowledge base does not include research that has confirmed or denied these theories in human participants. Due to the nature of both methods, this relationship should be explored to determine the effect on patients with muscle spasticity, including patients with dystonias.

Cerebral Palsy

Cerebral palsy is a debilitating disease that starts in infancy or young children.[22] Currently, it is the number one cause of childhood disabilities. The disease begins when damage occurs to the cerebral cortex either during fetal development, during birth, or after birth and is permanent. Types of damage could be periventricular leukomalacia, cerebral dysgenesis, intracranial hemorrhage or a lack of oxygen. It manifests in a variety of symptoms such as limb weakness, spasticity, crouched gait, ataxia and delays in reaching motor skill milestones. Every patient with cerebral palsy will have individualized presentation and severity of the disease. Doctors can diagnose the disease by testing motor skills, monitoring motor development and performing neuroimaging techniques like cranial ultrasounds, computed tomography (CT) and magnetic resonance imaging (MRI). While this disease is not curable, botulinum toxin has become a standard of treatment for cerebral palsy patients of all ages to help improve gait function by controlling spasms.

Nonpharmacologic options might include surgeries like rhizotomy to kill certain nerve roots responsible for cerebral

palsy or peripheral neurectomy to remove the nerves.[23] Orthopedic surgical options might include tendon lengthening or transfer, osteotomy or joint fusion to help with movement. Oral treatment options for cerebral palsy include dantrolene sodium, baclofen, tizanidine and benzodiazepines. Patients can also receive parenteral therapy to aid in chemical denervation, such as ethanol 45 to 100 percent, phenol 5 to 7 percent, botulinum toxin or intrathecal baclofen. Because not all patients are good surgical candidates, and botulinum toxin is not something a patient has to receive every day, it becomes a good option for many patients.

Children with cerebral palsy that affects their upper extremities often have spasticity patterns like internal shoulder rotation, elbow flexion, forearm pronation, wrist and finger flexion and thumb-in palm.[24] Many of these patients are not good candidates for surgery due to their age, so botulinum toxin therapy would be a good option to help control spasms until they are a better candidate for surgery. In a randomized, double-blind, placebo-controlled study of botulinum toxin A, researchers used the House Classification (HC) system to rate participants' functional ability. The participants received either botulinum toxin A or placebo at baseline, week 8, and week 20 if indicated. Visits were conducted at baseline and weeks 4, 8, 14, 20 and 26. At the visits where the patient received an injection, the patient met independently with both a physician and an occupational therapist, and if the visit did not include an injection, the patient was evaluated by just the occupational therapist. Doses were individualized to the patient, and if the physician felt that the patient did not need another injection the injection was not given at that appointment. The physician evaluated based on the Upper Extremity Rating scale (used to evaluate the range of motion of the limbs), the HC, and the Modified House Functional Classification. The occupational therapist used these same scales along with the Melbourne Assessment of Unilateral Upper Limb Function. The study also looked at Health-Related Quality of Life outcomes for the caregivers and also safety of botulinum toxin A by assessing any adverse events.

The study showed that the patients in the botulinum toxin A group had a statistically significant improvement in the Melbourne Assessment compared to placebo.[24] The study also showed a better improvement in the mean range of motion at weeks 20 and 26 for the botulinum toxin A group. There was not, however, any difference in the Health-Related Quality of Life data for the caregivers. Botulinum toxin A did prove to be relatively safe for the patients in the study with only mild to moderate adverse events reported such as muscle soreness at the injection site, muscle cramps, excessive weakness, headache, rash and fatigue. Overall, the study proved that botulinum toxin A is a good option for those patients with upper limb spasticity related to cerebral palsy that are not currently candidates for surgery.

In a similar randomized, placebo-controlled trial, botulinum toxin was compared with placebo in children with spastic hemiplegic upper limb cerebral palsy.[25] One of the major differences in the study was that the injections were combined with physiotherapy. The participants received injections at baseline and had follow-up visits at one, three and six months. The participants also had a physiotherapy program that included three (45 minute) weekly sessions for 24 weeks. The program included activities started out as unimanual and then moved bimanual and more complex as the study progressed. After the injection, participants received a customized positional splint. The study used the Assisting Hand Assessment (AHA) scale as a primary outcome to measure the use of the affected upper limb. Both the placebo group and the botulinum toxin A group showed improvement in the AHA score after receiving an injection and physiotherapy, but the botulinum toxin A group showed a faster and more substantial change. At the six month visit, the botulinum toxin group stopped showing improvement, while the placebo group continued to change. This correlates with other studies that concluded that the average length of effectiveness for botulinum toxin injections is around 12 weeks.[17] Because this study was small (only 27 participants), further studies need to be done on larger groups over a longer period of time; however, this study did confirm that botulinum toxin is effective in these patients, and that physiotherapy works as an adjunct when individualized to each patient.[25]

The treatment of cerebral palsy can vary due to the patient's needs. One common component of cerebral palsy treatment is exercise. It has been found that the inclusion of treadmill exercises benefits the symmetry, speed and endurance of cerebral palsy patients.[26] Spasticity of muscles results in weak lower extremity muscles and bone development due to the delay in independent ambulation. In a study of 37 children with diagnosed cerebral palsy, an experimental group completed treadmill sessions twice a week for three months in addition to rehabilitation programs twice a week. At the conclusion of the study, the results between the treadmill program participants and the control group, who did not exercise, were compared. Participants who completed treadmill exercise were able to walk significantly faster, longer and farther during the postparticipation testing ($p<0.001$). The results of this study supported the conclusion that had been found and documented previously; ambulation and exercise tolerance are improved with the inclusion of treadmill exercise. Various exercise methods were examined for effects on postural control of cerebral palsy patients in a meta-analysis performed by Dewar, Love and Johnston.[27] Treadmill training was supported as well as gross motor task training, hippotherapy, trunk-targeted training and reactive balance training.

In theory, the combination of exercise and botulinum toxin should compound the benefits of these treatments and reduce the potential adverse effect of nontargeted muscle weakness. In a study of 15 children, 10 weeks of a home strength program were performed three times a week in patients who also received Botulinum Type-A (BoNT-A) injections.[28] Significant results were documented in both groups that participated in the exercise program; one before the injections and the other after. The levels of muscle spasticity were reduced, in addition to increased strength in the exer-

cise and BoNT-A combined treatment group. As recorded in this study, the inclusion of exercise in conjunction with botulinum toxin injections can have a profound impact in cerebral palsy patients. Further research should continue to examine the timing, exercise method and other types of botulinum toxin for optimal treatment development.

Conclusion

Botulinum toxin has been established as an integral part in the treatment of disorders caused by muscle overactivity. Many clinical trials, shown in Table 2, have confirmed the safety and efficacy of its use. The benefits of the botulinum neurotoxin in the treatment of migraines, dystonias and cerebral palsy are only some of the uses for the toxin in the health care field. Botulinum toxin has also been included in the treatment of many ophthalmological disorders and movement disorders and continues to undergo testing for applications in smooth muscle overactivity disorders and hypersecretion of glands.[29] Although some adverse effects can occur, the discovery and use of this toxin has led to a higher quality of life for many patients with various disorders. The use of this drug in combination with other forms of treatment has the potential for even greater outcomes for patients. Further research will increase the impact botulinum toxin will have on the progression of treatments for disorders of spasticity.

References

1. Erbguth F. Historical notes on botulism, Clostridium botulinum, botulinum toxin, and the idea of the therapeutic use of the toxin. Mov Disord. 2004 Mar; 19(Suppl 8):S2-6.
2. Bentivoglio AR, Del Grande A, Petracca M, Ialongo T, Ricciardi L. Clinical differences between botulinum neurotoxin type A and B. Toxicon. 2015 Dec; 107:77-84.
3. Lexicomp [Internet]. Hudson (OH): Wolters Kluwer. 2016. Neuromuscular blocker agent, toxin; [2016; 20 Feb 2016]. Available from:0-online.lexi.com.polar.onu.edu/lco/action/search/pharmacat/patch_f?q=Neuromuscular+Blocker+Agent%2C+Toxin.
4. Dodick DW, Mauskop A, Elkind AH, DeGryse R, Brin MF, Silberstein SD. Botulinum toxin type A for the prophylaxis of chronic daily headache: subgroup analysis of patients not receiving other prophylactic medications: a randomized, double-blind, placebo-controlled study. Headache. 2005 April; 45:315-24.
5. DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. Pharmacotherapy: a pathophysiologic approach [Internet]. 9th ed. New York: McGraw-Hill; 2014. Chapter 45, Headache Disorders; [cited 2016 Feb 20]; [about 20 screens]. Available from:0-accesspharmacy.mhmedical.com.polar.onu.edu/content.aspx?bookid=689&sectionid=45310495.
6. Göksel, BK. The use of complementary and alternative medicine in patients with migraine. Noro Psikiyatr Ars (Archives of Neuropsychiatry). 2013 Sept; 41-6.
7. John PJ, Sharma N, Sharma CM, Kankane A. Effectiveness of yoga therapy in the treatment of migraine without aura: a randomized controlled trial. Headache. 2007 May; 47(5):654–61.
8. Narin S, Pinar L, Erbas D, Oztürk V, Idiman F. The effects of exercise and exercise-related changes in blood nitric oxide level on migraine headache. Clin Rehabil. 2003 Sept; 17(6):624-30.
9. Mitchell MP, Schaecher K, Cannon HE, Speckman M. Humanistic, utilization, and cost outcomes associated with the use of botulinum toxin for treatment of refractory migraine headaches in a managed care organization. J Manag Care Pharm. 2008 June; 14(5):442-50.
10. Albanese A, Asmus F, Bhatia KP, Elia AE, Elibol B, Filippini G, et al. EFNS guidelines on diagnosis and treatment of primary dystonias. Eur J Neurol. 2011; 18:5-18.
11. Albanese A, Lalli S. Is this dystonia? Mov Disord. 2009; 24(12):1725-31.
12. Albanese A, Barnes MP, Fernandez-Alvarez E, Fllippini G, Gasser T, Krauss JK, et al. A systematic review on the diagnosis and treatment of primary (idiopathic) dystonia and dystonia plus syndromes: report of an EFNS/MDS-ES task force. Eur J Neurol. 2006; 13:433-44.
13. Pappert EJ, Germanson T. Botulinum toxin type B vs. type A in toxin-naive patients with cervical dystonia: randomized, double-blind, noninferiority trial. Mov Disord. 2008; 23(4):510-17.
14. Jankovic J, Adler CH, Charles D, Comella C, Stacy M, Schwartz M, et al. Primary results from the cervical dystonia patient registry for observation of onabotulinumtoxinA efficacy (CD PROBE). J Neurol Sci. 2015; 349:84-93.
15. Evidente VGH, Fernandez HH, LeDoux MS, Branshear A, Grafe S, Hanschmann A, Comella CL. A randomized, double-blind study of repeated incobotulinumtoxinA (Xeomin) in cervical dystonia. J Neural Transm. 2013; 120:1699-707.
16. Truong D, Brodsky M, Lew M, Brashear A, Jankovic J, Molho E, et al. Long-term efficacy and safety of botulinum toxin type A (Dysport) in cervical dystonia. Parkinsonism Relat Disord. 2010; 16:316-23.
17. Dressler D, Tacik P, Saberi FA. Botulinum toxin therapy of cervical dystonia: comparing onabotulinumtoxinA (Botox) and incobotulinumtoxinA (Xeomin). J Neural Transm. 2014; 121:29-31.
18. Yun JY, Kim JW, Kim HT, Chung SJ, Kim JM, Cho JW, et al. Botox at a ratio of 2.5:1 units in cervical dystonia: a double-blind, randomized study. Mov Disord. 2015; 30(2): 206-13.
19. Jost WH, Hefter H, Stenner A, Reichel G. Rating scales for cervical dystonia: a critical evaluation of tools for outcome assessment of botulinum toxin therapy. J Neural Transm. 2013; 120(3):487-96.
20. Kazerooni R, Broadhead C. Cost-utility analysis of botulinum toxin type A products for the treatment of cervical dystonia. Am J Health-Syst Pharm. 2015; 72:301-7.
21. Tsai SW, Chen HL, Chang YC, Chen CM. Molecular mechanisms of treadmill therapy on neuromuscular atrophy induced via botulinum toxin A. Neural plasticity. 2013 Nov 12;2013.
22. National Institute of Neurological Disorders and Stroke [Internet]. Bethesda, MD: National Institute of Health; Cerebral palsy: hope through research; [updated 2016 Mar 16; cited 2016]; [about 12 screens]. Available from:www.ninds.nih.gov/disorders/cerebral_palsy/detail_cerebral_palsy.htm.
23. Koman LA, Paterson Smith B, Balkrishnan R. Spasticity associated with cerebral palsy in children: guidelines for the use of botulinum A toxin. Paediatr Drugs. 2003; 5(1):11-23.
24. Koman LA, Smith BP, Williams R, Richardson R, Naughton M, Griffin L, Evans P. Upper extremity spasticity in children with cerebral palsy: a randomized, double-blind, placebo-controlled study of the short-term outcomes of treatment with botulinum a toxin. J Hand Surg. 2013; 38A:435-46.
25. Ferrari A, Maoret AR, Muzzini S, Alboresi S, Lombardi F, Sgandurra G, et al. A randomized trial of upper limb botulinum toxin versus placebo injection, combined with physiotherapy, in children with hemiplegia. Res Dev Disabil. 2014; 35:2505-13.
26. Saritaş N, Abakay H, Karakuş M, Coşkun B. Somatotype profiles and changes depending on treadmill exercise in children with cerebral palsy. Journal of Physical Education & Sports Science. 2014 Aug; 8 (2):207-14.
27. Dewar R, Love S, Johnston L. Exercise interventions improve postural control in children with cerebral palsy: a systematic review. Dev Med Child Neurol. 2015 June; 57(6):504-20.
28. Williams SA, Elliott C, Valentine J, Gubbay A, Shipman P, Reid S. Combining strength training and botulinum neurotoxin intervention in children with cerebral palsy: the impact on muscle morphology and strength. Disabil Rehabil. 2013 April; 35(7): 596-605.
29. Münchau A, Bhatia KP. Uses of botulinum toxin injection in medicine today. BMJ (Int Ed). 2000 Jan 15; 320(7228):161–5.

The authors have no conflict of interest or funding support to disclose.